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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/249,529	02/12/99	MARKS J	02307E-08521

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EXAMINER	
PONNALURI,P	
ART UNIT	**PAPER NUMBER**
1627	13

DATE MAILED: 08/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/249,529	Applicant(s) Marks et al
	Examiner P. Ponnaluri	Group Art Unit 1627

☒ Responsive to communication(s) filed on *May 8, 2000* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-50* is/are pending in the application.

Of the above, claim(s) *18-50* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-17* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6, 8*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. This application claims priority to provisional application 60/082,953, filed on 4/24/98.

2. Claims 1-50 are currently pending in this application.

3. The amendment filed on 5/8/00 has been fully considered and entered into the application.

4. Applicant's election with traverse of group I, claims 1-17, in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the restriction between groups I and II is unnecessary. Applicants argue that even though the groups are directed to distinct inventions, they should be examined together. Applicants argue that the group I is drawn to a method of identifying internalizing antibodies, and group II inventions are drawn to the use of the identified internalizing antibodies of group I to detect internalizing receptors. Applicants argue that the prior art for group I is relevant to group II methods, thus it is not great burden to search both groups I and II together. This is not persuasive, because group I inventions different from group II inventions. The group I inventions are drawn to a method of selecting polypeptide or antibody moieties which are internalized into target cells and group II inventions are drawn to a method of internalizing receptor, and also the group II method has additional method steps. Thus, the restriction among groups I and II is proper.

Applicants argue that the restriction among the groups III and IV should be withdrawn. Applicants argue that the search for multivalent antibody phage display library of group III identifies prior art which would be relevant to nucleic acids library of group IV . This is not found persuasive because group IV inventions are drawn to nucleic acid library not 'nucleic acids

encoding group III multivalent antibody phage display library' as applicants have pointed out. The nucleic acid library which encodes an antibody library of group IV may or may not encode the multivalent antibody phage display library of group III . Thus restriction among groups III and IV is proper.

The requirement is still deemed proper and is therefore made **FINAL.**

5. Claims 18-50 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected inventions, the requirement having been traversed in Paper No. 12.

6. Claims 1-17 are currently being examined in this application.

7. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Applicant is invited to notice that boxes 5 and 12 were checked by the draftsman. If applicants renumber the figures, applicant is encouraged to amend the specification so that the description of renumbered figures corresponds to the renumbered figures.

8. The use of the trademark TWEEN 20 (page 13, line 2), BIO-RAD (page 48, line 27), LIPOFECTAMINE (page 61, line 6) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

9. Claim 1 is objected to because of the following informalities: claim 1 recites in step (ii), 'a cells', applicants are requested to amend the claim as "cells of" . Appropriate correction is required.

10. Claims 1-17 are e rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite by reciting 'antibody binding moieties'. It is not clear whether the claim is directed to identifying antibody or antibody binding moieties. Applicants are requested to clarify, because antibodies and antibody binding moieties are different. Several proteins or ligands would read on the antibody binding moieties. From the specification disclosure, and the dependent claims it is understood that the method is drawn to selection of antibodies. For compact prosecution, in the absence of clear definition of 'antibody binding moieties' in the specification, the claim is interpreted as 'a method of selecting antibodies or polypeptides.'

Claim 1 is vague and indefinite by reciting in step I), contacting target cells with members of phage display library. It is not clear which phage display library applicants are referring to. The specification discloses antibody phage display library, thus the claim is interpreted as antibody phage display library is contacted with target cells. Applicants are requested to clarify whether (the the polypeptide or antibody that internalize into target cells) a specific polypeptide is

displayed on the phage or the phage displays any polypeptide is used in the instant method. Applicants are requested to clarify.

Claim 1 is vague and indefinite by reciting in step iv) '...where members of said phage display library can be internalized if bound to an internalizing marker..', the recitation of 'can be' is indefinite, and 'if bound to' is vague. The specification discloses that the 'internalizing marker' is a molecule present on the external cell surface. Does it mean that the members of phage library is internalized when they are bound to an external cell surface marker. But it is not clear how the phage binding to the marker is determined. Applicants have not shown what would happen if the phage display are not bound to the external marker; and also the claim is vague because the in step v), the recitation of '...if members of said phage display are internalized...' Applicants are requested to clarify.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 92/20791 (Winter et al) in view of either Ewjik et al (Proc. Natl. Acad. Sci. USA, vol. 94, pp 3903-3908, April 1997) or Stausbol-Gron et al (FEBS Letters, vol. 39., pages 71-75, 1996).

The instant claims recite a method of selecting polypeptide or antibody that are internalized into target cells comprising contacting the members of phage display library with target cells; contacting the members of phage display library with cells of subtractive cell line, removing the non-specifically bound phage display library; culturing the target cells under conditions such that the members of phage display library are internalized; and identifying the internalized members of phage display library.

Winter et al teach a method for producing members of specific binding pairs (sbp) (refers to the polypeptide or antibody that are internalized of the instant claims). The reference teaches that population of polypeptide chain components of sbp members are combined to form a library of sbps displayed by secreted replicable genetic display packages (rgdp) (refers to phage display library of the instant claims) (i.e., see the abstract). The reference teaches that the rgdps may be virus such as bacteriophage (see page 13, in particular). The reference teaches the use of rgdps in targeted gene transfer (see page 12, in particular). The reference teaches that the rgdps carry sequences directed to expression of tumor suppressing gene or gene product designed to toxic to

the target cell (see page 12, lines 22-28, in particular). The reference teaches that the rgdps may be contacted with a particular cell (bacteria or a tumor cell) or group of cells (refers to the instant claim 15), and the phage is internalized (see page 12, line 8, in particular), and the phage genome is expressed under suitable conditions, the sequence expressed contains a detectable gene product (refers to phage carries a gene encoding a detectable product or selectable product of the instant claims) such as luciferase (see line 21, in particular), and the cell or cells that express the luciferase gene is detected by the light they emit (see page 12, lines 49-51, in particular) (refers to instant claims 7, 12-14 of the instant claims). The reference teaches that the individual rgdps expressing the desired specificity can be isolated from the library using known screening techniques such as microscopy or biosensor and the nucleic acid of the peptide is recovered by the use of PCR. The reference teaches that the targeted gene transfer technique has number of uses in research, in therapy and in diagnostics.

The claimed invention differs from the prior art teachings by reciting that the phage display library members which are non-specifically bound to target cells are removed using subtractive cell line. Winter et al teach that the phage display library carry sequences directed to expression of tumor suppressing gene or gene product designed to toxic to the target cell, and the phage is internalized , and the phage genome is expressed under suitable conditions, the sequence expressed contains a detectable gene product. Winter et al do not teach the use of subtractive cell line to remove the non specifically bound phage particles to the target cells. However, either Ewijk et al or Stausbol-Gron et al teach phage display subtraction method. Ewijk et al teach

subtractive isolation of phage-displayed single-chain antibodies to thymic stromal cells by intact thymic fragments. The reference teaches the use of phage antibody display technology with specific aim to isolate thymic stromal cell specific single chain antibodies from a phage library. A subtractive approach using intact, midly fixed thymic fragments as target tissue and thymocytes and spleen cells used to remove undesired specificities of the phage antibody library. The reference teaches that the phage library was incubated with thymocytes and spleen cells; to this target cells (thymic fragments) have added and incubated at 4^0 C. The following day the supernatant was removed and the target cells were washed to remove nonspecifically adhered phages. The specifically bound phage and thymic fragments were cultured at 37^0 C, and the specific phage was identified. The reference teaches that the subtractive isolation using thymocytes and splenocytes as adsorber cells, and using thymic cells as target cells, they were able to isolate monoclonal phage antibodies reactive with thymic stromal cell types, while monoclonal phage antibodies to lymphoid cells were not detected.

Stausbol-Gron et al teach phage display subtraction method with potential for analysis of differential gene expression. The reference teaches that a competitive bio-panning procedure was developed and tested on two model systems using a phagemid library of single chain Fv antibody fragments. The reference teaches that the phage library was incubated with targets and competitive proteins at 4^0 C, and the bound phage was eluted and propagated at 37^0 C. The reference teaches that the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids. The reference teaches

that the subtractive strategy is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells. Thus, it would have been obvious to a person of ordinary skill in the art to use the subtractive isolation of phage displayed single chain antibodies to remove nonspecifically bound members of phage library as taught by Ewijk et al or the subtraction method taught by Stausbol-Gron et al with the method of Winter et al to identify phage display members which transfer (or internalize) the specific gene to target cells, because Winter et al teach individual rgdps expressing the desired specificity can be isolated from the library, and targeted gene transfer technique has number of uses in research, in therapy and in diagnostics, Ewijk et al teach that the phage display technology can be applied to isolate scFvs directed to specific cell types in presence of other kinds of cells and Stausbol-Gron et al teach that the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids and it is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells.

13. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barry et al (Nature Medicine, vol. 2, no. 3, March 1996, pages 299-305) in view of either Ewjik et al (Proc. Natl. Acad. Sci. USA, vol. 94, pp 3903-3908, April 1997) or Stausbol-Gron et al (FEBS Letters, vol. 39., pages 71-75, 1996).

Barry et al teach a method to generate cell targeting ligands using peptide presenting phage libraries to select peptides that bind and enter several different cell types. The reference

teaches peptide presenting phage libraries (random amino acids) fused to the amino terminus of the pIII protein. The reference teaches a method to identify the cells which bind to the phage and the selected phage or peptide sequence is determined. The reference teaches that the peptide presenting phage are useful as gene delivery vehicles. The reference teaches that the phage bearing the peptide and a luciferase (detectable product or selectable product of the instant claims) plasmid (refers to instant claim 24) is used to mediate transfection of fibroblast cells, and the bacteriophage is useful in gene therapy.

The claimed invention differs from the prior art teachings by reciting method of removal of non specific binding of phage display library members to target cells by using subtractive strategy. Barry et al teach method to generate cell targeting ligands and a method to identify the cells that bind to phage. Barry et al do not teach the use of subtractive strategy to eliminate non specific binding of phage members to target cells. However, However, either Ewijk et al or Stausbol-Gron et al teach phage display subtraction method.

Stausbol-Gron et al teach phage display subtraction method with potential for analysis of differential gene expression. The reference teaches that a competitive bio-panning procedure was developed and tested on two model systems using a phagemid library of single chain Fv antibody fragments. The reference teaches that the phage library was incubated with targets and competitive proteins at 4^0 C, and the bound phage was eluted and propagated at 37^0 C. The reference teaches that the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids. The reference teaches

that the subtractive strategy is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells.

Ewijk et al teach subtractive isolation of phage-displayed single-chain antibodies to thymic stromal cells by intact thymic fragments. The reference teaches the use of phage antibody display technology with specific aim to isolate thymic stromal cell specific single chain antibodies from a phage library. A subtractive approach using intact, midly fixed thymic fragments as target tissue and thymocytes and spleen cells used to remove undesired specificities of the phage antibody library. The reference teaches that the phage library was incubated with thymocytes and spleen cells; to this target cells (thymic fragments) have added and incubated at 4^0 C. The following day the supernatant was removed and the target cells were washed to remove nonspecifically adhered phages. The specifically bound phage and thymic fragments were cultured at 37^0 C, and the specific phage was identified. The reference teaches that the subtractive isolation using thymocytes and splenocytes as adsorber cells, and using thymic cells as target cells, they were able to isolate monoclonal phage antibodies reactive with thymic stromal cell types, while monoclonal phage antibodies to lymphoid cells were not detected.

Thus, it would have been obvious to a person of ordinary skill in the art to use the subtractive isolation of phage displayed single chain antibodies to remove nonspecifically bound members of phage library as taught by Ewijk et al or the subtraction method taught by Stausbol-Gron et al with the method of Larocca et al (Barry) to identify phage display members which transfer (or internalize) the specific gene to target cells, because Barry et al teach individual phage bearing

the specific peptide can be isolated from the library using luciferase, the phage bearing the specific peptide is useful in gene therapy, Ewijk et al teach that the phage display technology can be applied to isolate scFvs directed to specific cell types in presence of other kinds of cells and Stausbol-Gron et al teach that the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids and it is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells. The person of ordinary skill in the art would have been motivated to use the subtractive strategy in the method of gene transfer taught by Barry et al with the expectation of eliminating non specific binding of members of phage display library with target cells.

14. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,054,312 (Larocca et al) (filing date 29 August, 1997) in view of either Ewjik et al (Proc. Natl. Acad. Sci. USA, vol. 94, pp 3903-3908, April 1997) or Stausbol-Gron et al (FEBS Letters, vol. 39., pages 71-75, 1996).

Larocca et al teach receptor mediated gene delivery using bacteriophage vectors. The reference teaches that a library of random peptides is engineered into gene VII protein of a phage vector that has ligand fused to gene III and that carries a detectable (e.g., GFP) or selectable marker. Mammalian cells are infected with the library and the cells selected by detection of the marker. The cells that have the highest expression have been recovered, and the peptide genes are encoded into the phage vectors. The reference teaches fusion proteins comprise gene encoding all or a receptor-binding polypeptide portion of a ligand (or mAb, Fab) genetically fused or linked to

coat protein encoding gene of a bacteriophage particle. The reference teaches that the nucleotide sequences encoding the ligand-phase fusions may be further modified via insertion of a mammalian reporter gene, in order to further verify binding and internalization, as well expression of the nucleic acid. The reference teaches that the reporter gene is EGFP, which is translated into green fluorescent protein (GFP) when gene delivery and expression occur.

The claimed invention differs from the prior art teachings by reciting method of removal of non specific binding of phage display library members to target cells by using subtractive strategy. Barry et al teach method to generate cell targeting ligands and a method to identify the cells that bind to phage. However, either Ewijk et al or Stausbol-Gron et al teach phage display subtraction method. Ewijk et al teach subtractive isolation of phage-displayed single-chain antibodies to thymic stromal cells by intact thymic fragments. The reference teaches the use of phage antibody display technology with specific aim to isolate thymic stromal cell specific single chain antibodies from a phage library. A subtractive approach using intact, midly fixed thymic fragments as target tissue and thymocytes and spleen cells used to remove undesired specificities of the phage antibody library. The reference teaches that the phage library was incubated with thymocytes and spleen cells; to this target cells (thymic fragments) have added and incubated at 4^0 C. The following day the supernatant was removed and the target cells were washed to remove nonspecifically adhered phages. The specifically bound phage and thymic fragments were cultured at 37^0 C, and the specific phage was identified. The reference teaches that the subtractive isolation using thymocytes and splenocytes as adsorber cells, and using thymic cells as target cells, they

were able to isolate monoclonal phage antibodies reactive with thymic stromal cell types, while monoclonal phage antibodies to lymphoid cells were not detected.

Stausbol-Gron et al teach phage display subtraction method with potential for analysis of differential gene expression. The reference teaches that a competitive bio-panning procedure was developed and tested on two model systems using a phagemid library of single chain Fv antibody fragments. The reference teaches that the phage library was incubated with targets and competitive proteins at 4^0 C, and the bound phage was eluted and propagated at 37^0 C. The reference teaches that the subtractive panning strategy is fast and easy way to identify research reagents directed against biomarkers of cellular extracts or biological fluids. The reference teaches that the subtractive strategy is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells. Thus, it would have been obvious to a person of ordinary skill in the art to use the subtractive isolation of phage displayed single chain antibodies to remove nonspecifically bound members of phage library as taught by Ewijk et al or the subtraction method taught by Stausbol-Gron et al with the method of Larocca et al to identify phage display members which transfer (or internalize) the specific gene to target cells, because Larocca teach individual phage which express the peptide of interest can be isolated from the library, and targeted gene transfer technique has number of uses in research, in therapy and in diagnostics, Ewijk et al teach that the phage display technology can be applied to isolate scFvs directed to specific cell types in presence of other kinds of cells and Stausbol-Gron et al teach that the subtractive panning strategy is fast and easy way to identify research reagents directed

against biomarkers of cellular extracts or biological fluids and it is valuable in attempts to identify antibodies against known or unknown antigens in a given population of cells.

15. No claims are allowed.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner can normally be reached on Monday to Thursday from 6.30 AM to 4.00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venakt, Ph.D., can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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